

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-16660	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/006723	International filing date (day/month/year) 02/03/2005	(Earliest) Priority Date (day/month/year) 15/03/2004
Applicant ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).



- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2.



Certain claims were found unsearchable (See Box II).

3.



Unity of invention is lacking (see Box III).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.



- b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/006723

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/56 C07C317/32 C07C233/25 C07C217/90 C07C233/73
 C07C235/18 C07C323/41 C07D213/82 C07D307/68 C07D295/20
 C07D261/18 C07D333/38 C07D231/14 C07D285/06 C07D241/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, WPI Data, BEILSTEIN Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	✓ WO 03/002519 A (BAYER AKTIENGESELLSCHAFT; SCHMECK, CARSTEN; MUELLER, ULRICH; SCHMIDT,) 9 January 2003 (2003-01-09) page 33; claim 1	1,2,4,6,7,11-15,17
X	✓ FR 2 291 743 A (ROUSSEL UCLAFF) 18 June 1976 (1976-06-18) the whole document	1,2,4,6-9,11-15,17
X	✓ WO 02/12224 A (ORTHO MCNEIL PHARMACEUTICAL, INC) 14 February 2002 (2002-02-14) examples 6-9 claims 1,23 ----- -/-	1-9,11-15,17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
 E earlier document but published on or after the international filing date
 L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 O document referring to an oral disclosure, use, exhibition or other means
 P document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 & document member of the same patent family

Date of the actual completion of the international search

1 August 2005

Date of mailing of the international search report

22/08/2005

Name and mailing address of the ISA

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Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US2005/006723

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 20, 10 July 2001 (2001-07-10) ✓ - & JP 2001 064176 A (SUMITOMO PHARMACEUT CO LTD; SUMITOMO CHEM CO LTD), 13 March 2001 (2001-03-13) abstract	1,2,4, 6-9, 11-15,17
X	✓ WO 00/59878 A (ICOS CORPORATION; FOWLER, KERRY; ORME, MARK; STAUNTON, DONALD, E; ADOL) 12 October 2000 (2000-10-12) claims 1,7	1-9,11
X	✓ EP 1 113 000 A (AJINOMOTO CO., INC) 4 July 2001 (2001-07-04) claim 1; examples	1,2,4, 6-9,11
X	✓ EP 1 193 255 A (AJINOMOTO CO., INC) 3 April 2002 (2002-04-03) claim 1; examples	1-3,5-9, 11
X	✓ US 5 084 449 A (SEYDEL ET AL) 28 January 1992 (1992-01-28) claims	1,2,4, 6-9,11
X	✓ US 3 976 784 A (COLES ET AL) 24 August 1976 (1976-08-24) claims	1,2,4, 6-9,11
X	✓ US 2 456 258 A (DOHRN MAX ET AL) 14 December 1948 (1948-12-14) claims	1-3,5-9, 11
X	✓ WENNER, WILHELM: "4-Aminomethyl-4'-aminodiphenyl sulfone and related compounds" JOURNAL OF ORGANIC CHEMISTRY, 22, 1508 -13 CODEN: JOCEAH; ISSN: 0022-3263, 1957, XP002338658 page 1512; table III	1,2,4, 6-9,11
X	✓ SURREY, A. R. ET AL: "Sulfides and sulfones of pyridine and quinoline" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 62, 173 -4 CODEN: JACSAT; ISSN: 0002-7863, 1940, XP002338659 table 1	1-3,5-9, 11
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 21, 3 August 2001 (2001-08-03) ✓ - & JP 2001 089412 A (OTSUKA PHARMACEUT CO LTD), 3 April 2001 (2001-04-03) ex. 109,209,211,212 abstract	1-9,11
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>✓ US 5 883 096 A (LOWE ET AL) 16 March 1999 (1999-03-16) claim 1; example 747</p> <p>-----</p>	1-9,11
X	<p>✓ EP 0 407 346 A (CIBA-GEIGY AG) 9 January 1991 (1991-01-09) page 15</p> <p>-----</p>	1-3,5-9
X	<p>✓ DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1951, TAKAHASHI ET AL.: "Pyridine derivatives containing sulfur IV. Synthesis of nitro- and aminopyridines" XP002338663 retrieved from STN Database accession no. 1951:26999 abstract & YAKUGAKU ZASSHI , 62, 488-91 CODEN: YKKZAJ; ISSN: 0031-6903, 1942,</p> <p>-----</p>	1-3,5-9
X	<p>✓ DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1963, ACHARYA ET AL.: "Synthesis of substituted phenyl 2-pyridyl ethers" XP002338664 retrieved from STN Database accession no. 1963:14812 abstract & JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, SECTION B: PHYSICAL SCIENCES , 21B, 452-4 CODEN: JSIBAW; ISSN: 0368-4210, 1962,</p> <p>-----</p>	1-3,5-9
A	<p>✓ WO 99/33806 A (ORTHO-MCNEIL PHARMACEUTICAL, INC; CARSON, JOHN, R; CARMOSIN, RICHARD,) 8 July 1999 (1999-07-08) claim 1</p> <p>-----</p>	1-17
P,X	<p>✓ WO 2004/093800 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA; OREGON HEALTH & SCIENCE U) 4 November 2004 (2004-11-04) pages 8,45; claim 1</p> <p>-----</p>	1,2,4, 6-9, 11-15,17
P,X	<p>✓ WO 2004/026305 A (ELI LILLY AND COMPANY; BLANCO-PILLADO, MARIA-JESUS; CHAPPELL, MARK, DO) 1 April 2004 (2004-04-01) page 232; example 381d</p> <p>-----</p>	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/006723

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/006723

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			IE 58394 B1	08-09-1993
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			JP 60255760 A	17-12-1985
			KR 9307846 B1	20-08-1993
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			OA 8023 A	31-01-1987
			PH 22698 A	14-11-1988
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			DE 2504596 A1	14-08-1975
			DK 35175 A	22-09-1975
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			JP 50135210 A	27-10-1975
			LU 71792 A1	19-08-1976
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/006723

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			US 6288068 B1	11-09-2001
			US 5889006 A	30-03-1999
			US 2002103205 A1	01-08-2002
			AT 258170 T	15-02-2004
			AU 701452 B2	28-01-1999
			AU 4971796 A	11-09-1996
			CA 2212895 A1	29-08-1996
			DE 69631370 D1	26-02-2004
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			EP 0407346 A2	09-01-1991
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			JP 2001527068 T	25-12-2001
			TW 476755 B	21-02-2002
			WO 9933806 A1	08-07-1999
			ZA 9811842 A	23-06-2000
WO 2004093800	A	04-11-2004	US 2005096485 A1	05-05-2005
			WO 2004093800 A2	04-11-2004
WO 2004026305	A	01-04-2004	AU 2003269980 A1	08-04-2004
			BR 0314308 A	05-07-2005
			CA 2499690 A1	01-04-2004
			WO 2004026305 A1	01-04-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

15 DEC 2005 / 15 JAN 2006

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference

see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No

PCT/US2005/006723

International filing date (day/month/year)

02.03.2005

Priority date (day/month/year)

15.03.2004

International Patent Classification (IPC) or both national classification and IPC

C07C217/56, C07C317/32, C07C233/25, C07C217/90, C07C233/73, C07C235/18, C07C323/41, C07D213/82,

Applicant

ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/006723

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/006723

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 12-16

because:

- ☒ the said international application, or the said claims Nos. 12-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/006723

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	10,16
	No: Claims	1-9,11-15,17
Inventive step (IS)	Yes: Claims	10,16
	No: Claims	1-9,11-15,17
Industrial applicability (IA)	Yes: Claims	1-11,17
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) The present application relates to diaryl ethers and analogues thereof useful as opioid antagonists (see table 1, pages 25-26).

2) The following documents are cited:

D1: WO 03/002519 A
D2: FR-A-2 291 743
D3: WO 02/12224 A
D4: JP 2001 064176 A
D5: WO 00/59878 A
D6: EP-A-1 113 000
D7: EP-A-1 193 255
D8: US-A-5 084 449
D9: US-A-3 976 784
D10: US-A-2 456 258
D11: J.ORG.CHEM., 22, 1508 -13
D12: J.AM.CHEM.SOC., 62, 173 -4
D13: JP 2001 089412 A
D14: US-A-5 883 096
D15: EP-A-0 407 346
D16: CAPLUS [Online] accession no. 1951:26999
D17: CAPLUS [Online] accession no. 1963:14812
D18: WO 99/33806 A
D19: WO 2004/093800 A
D20: WO 2004/026305 A

Documents D19 and D20 were published after the priority claimed for the present application; on the presumption that the priority is validly claimed, these documents are not considered as prior art.

3) Search limitation

The initial phase of the search revealed such a great amount of documents relevant to the novelty of claims 1,2,4,6-9 and 11, that only a limited number of representative documents has been cited.

4) Novelty

The subject-matter of claims 1-9, 10-15 and 17 is considered anticipated by documents D1-D17 as cited in the search report.

In this context it is noted that the therapeutical indications of claims 12-15 and 17 are so broad, that the various indications mentioned in for instance D1-D4 may be considered as anticipating.

5) Inventive step

In as far as the claimed subject-matter is novel, i.e. relates to truly new compounds (e.g. claim 10) or truly new indications (e.g. claim 16) the claimed subject-matter may be considered to involve an inventive step.

Closest prior art seems D18 describing similar activity for biaryl amino piperidines. It could not be foreseen that the present compounds provide for alternative agents with respect to D18.

6) Further observations

Claims 12-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Claim 5 is unclear in its formulation as it actually seems to comprise the features of two different claims.